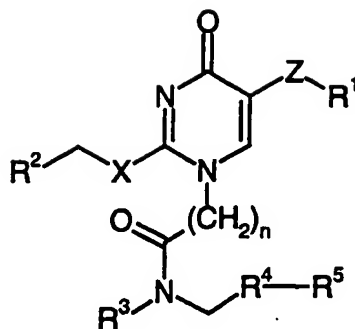


Claims

1. A compound of formula (I):



(I)

in which:

R^1 is an aryl or heteroaryl group, optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from $C_{(1-18)}$ alkyl, $C_{(1-18)}$ alkoxy, $C_{(1-18)}$ alkylthio, aryl $C_{(1-18)}$ alkoxy, hydroxy, halogen, CN, COR^6 , carboxy, $COOR^6$, $CONR^9R^{10}$, NR^6COR^7 , $SO_2NR^9R^{10}$, $NR^6SO_2R^7$, NR^9R^{10} , mono to perfluoro- $C_{(1-4)}$ alkyl and mono to perfluoro- $C_{(1-4)}$ alkoxy, or, as a single substituent, optionally in combination with a further substituent as hereinbefore defined, CH_2COOH or a salt thereof, CH_2COOR^8 , $CH_2CONR^9R^{10}$, CH_2CN , $(CH_2)_mNR^9R^{10}$, $(CH_2)_mOH$ or $(CH_2)_mOR^6$ where m is an integer from 1 to 3;

R^2 is an aryl or heteroaryl group, optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from $C_{(1-18)}$ alkyl, $C_{(1-18)}$ alkoxy, $C_{(1-18)}$ alkylthio, aryl $C_{(1-18)}$ alkoxy, hydroxy, halogen, CN, COR^6 , carboxy, $COOR^6$, $CONR^9R^{10}$, NR^6COR^7 , $SO_2NR^9R^{10}$, $NR^6SO_2R^7$, NR^9R^{10} , mono to perfluoro- $C_{(1-4)}$ alkyl, mono to perfluoro- $C_{(1-4)}$ alkoxy, and aryl $C_{(1-4)}$ alkyl;

R^3 is hydrogen or $C_{(1-4)}$ alkyl which may be unsubstituted or substituted by hydroxy, OR^6 , COR^6 , carboxy, $COOR^6$, $CONR^9R^{10}$, NR^9R^{10} , mono- or di-(hydroxy $C_{(1-6)}$ alkyl)amino or N-hydroxy $C_{(1-6)}$ alkyl-N- $C_{(1-6)}$ alkyl amino;

R^4 is an aryl or a heteroaryl ring optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from $C_{(1-18)}$ alkyl, $C_{(1-18)}$ alkoxy, $C_{(1-18)}$ alkylthio, aryl $C_{(1-18)}$ alkoxy, hydroxy, halogen, CN, COR^6 , carboxy, $COOR^6$, $CONR^9R^{10}$, NR^6COR^7 , $SO_2NR^9R^{10}$, $NR^6SO_2R^7$, NR^9R^{10} , mono to perfluoro- $C_{(1-4)}$ alkyl and mono to perfluoro- $C_{(1-4)}$ alkoxy;

R^5 is an aryl ring which is further optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from $C_{(1-18)}$ alkyl, $C_{(1-18)}$ alkoxy, $C_{(1-18)}$ alkylthio, aryl $C_{(1-18)}$ alkoxy, hydroxy, halogen, CN, COR^6 , carboxy, $COOR^6$, $CONR^9R^{10}$, NR^6COR^7 , $SO_2NR^9R^{10}$, $NR^6SO_2R^7$, NR^9R^{10} , mono to perfluoro- $C_{(1-4)}$ alkyl and mono to perfluoro- $C_{(1-4)}$ alkoxy;

R^6 and R^7 are independently hydrogen or $C_{(1-20)}$ alkyl, for instance $C_{(1-4)}$ alkyl (e.g. methyl or ethyl);

R^8 is $C_{(1-4)}$ alkyl or a pharmaceutically acceptable *in vivo* hydrolysable ester group;

R^9 and R^{10} which may be the same or different is each selected from hydrogen, $C_{(1-12)}$ alkyl, CH_2R^{11} , $CHR^{12}CO_2H$ or a salt thereof, or R^9 and R^{10} together with the nitrogen to which they are attached form a 4- to 7-, preferably 5- to 7-, membered ring optionally containing one or more further heteroatoms selected from oxygen, nitrogen and sulphur, and optionally substituted by one or two

substituents selected from hydroxy, oxo, $C_{(1-4)}$ alkyl, $C_{(1-4)}$ alkylCO, aryl, e.g. phenyl, or aralkyl, e.g. benzyl, for instance morpholine or piperazine;

R^{11} is COOH or a salt thereof, COOR⁸, CONR⁶R⁷, CN, CH₂OH or CH₂OR⁶;

R^{12} is an amino acid side chain such as CH₂OH from serine;

5 n is an integer from 1 to 4, preferably 1 or 3;

X is O or S; and

Z is CR¹³R¹⁴ where R¹³ and R¹⁴ are each hydrogen or $C_{(1-4)}$ alkyl, or R¹³ and R¹⁴ together with the intervening carbon atom form a $C_{(3-6)}$ cycloalkyl ring.

10 2. A compound of formula (I) as claimed in claim 1 in which Z is CH₂.

3. A compound of formula (I) as claimed in claim 1 or 2 in which R¹ is an aryl group selected from phenyl and naphthyl or a heteroaryl group which comprises a 5- or 6- membered, monocyclic heteroaryl group comprising 1 or 2 nitrogen heteroatoms.

15 4. A compound of formula (I) as claimed in any one of claims 1 to 3 in which R¹ is pyrimidyl optionally substituted by 1 or 2 substituents selected from oxo, aryl $C_{(1-4)}$ alkyl, $C_{(1-6)}$ alkyl, $C_{(3-6)}$ cycloalkyl, hydroxy, $C_{(1-4)}$ alkoxy, carboxy $C_{(1-6)}$ alkyl, $C_{(1-6)}$ alkylcarboxy $C_{(1-6)}$ alkyl, di- $C_{(1-6)}$ alkylamino, and morpholino; or pyrazolyl optionally substituted by $C_{(1-6)}$ alkyl.

20 5. A compound as claimed in claim 4 in which ZR¹ is pyrimid-5-ylmethyl optionally substituted by 2-methoxy, 2-trifluoromethyl, 2-(4-morpholino) or 2-dimethylamino; 2-oxo-pyrimid-5-ylmethyl or 1-methyl-4-pyrazolylmethyl.

25 6. A compound of formula (I) as claimed in any one of claims 1 to 6 in which X is S.

7. A compound of formula (I) as claimed in any one of claims 1 to 6 in which R² is an aryl group selected from phenyl and naphthyl or a heteroaryl group selected from pyridyl, pyrimidinyl, pyrazolyl, furanyl, thienyl, thiazolyl, quinolyl, benzothiazolyl, pyridazolyl and pyrazinyl.

30 8. A compound of formula (I) as claimed in claim 7 in which R² is phenyl optionally substituted by halogen

35 9. A compound of formula (I) as claimed in any one of claims 1 to 8 in which R³ is selected from hydrogen; and methyl, ethyl and propyl, optionally substituted by amino, $C_{(1-3)}$ alkylamino, di- $C_{(1-3)}$ alkylamino, hydroxy $C_{(1-3)}$ alkylamino, hydroxy, $C_{(1-3)}$ alkoxy, carboxy, $C_{(1-3)}$ alkylcarboxy, and heterocycl.

40 10. A compound of formula (I) as claimed in any one of claims 1 to 9 in which R⁴ is selected from phenyl optionally substituted by halogen; thiophene; pyridine; and pyrimidine.

11. A compound of formula (I) as claimed in any one of claims 1 to 10 in which R⁵ is phenyl optionally substituted by halogen, trifluoromethyl, or trifluoromethoxy.

12. A compound of formula (I) as claimed in claim 10 or 11 in which R⁴ and R⁵ together form a 4-(phenyl)phenyl substituent in which the remote phenyl ring may be optionally substituted by halogen or trifluoromethyl.

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13. A compound of formula (I) as claimed in claim 1 and as named in any one of Examples 1 to 157.

14. A compound of formula (I) as claimed in claim 13 selected from:

- 10 1-(N-Methyl-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one;
1-(N-Methyl-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one;
1-(N-(2-Dimethylaminoethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one;
15 1-(N-Methyl-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-(4-morpholino)pyrimidin-5-ylmethyl)pyrimidin-4-one;
1-(N-(2-(dimethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one;
1-(N-(2-(diethylamino)ethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one;
20 1-(N-(2-(diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyridin-5-ylmethyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one;
1-(N-(2-(1-Piperidino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one bitartrate;
25 1-(N-(Carboxymethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one sodium salt; and
1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one or a pharmaceutically acceptable salt thereof, including the hydrochloride, bitartrate, citrate and tosylate salts.

30

15. A pharmaceutical composition comprising a compound of formula (I) as claimed in any one of the preceding claims and a pharmaceutically acceptable carrier.

16. A compound of formula (I) as claimed in claim 1 for use in therapy.

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17.. The use of a compound of formula (I) as claimed in claim 1 for the manufacture of a medicament for treating atherosclerosis.

18. A method of treating a disease state associated with activity of the enzyme Lp-PLA₂ which method involves treating a patient in need thereof with a therapeutically effective amount of a compound of formula (I) as claimed in claim 1.

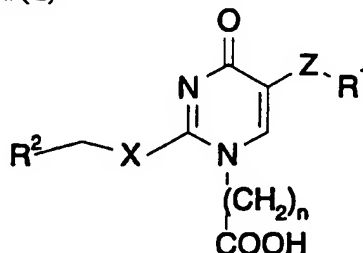
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19. A method of treating atherosclerosis which method comprises administering to a patient in need thereof an effective amount of a compound of formula (I) as claimed in claim 1 and a statin.

20. A process for preparing a compound of formula (I) as defined in claim 1 which process comprises:

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(a) reacting a compound of formula (II):



(II)

in which X, Y, Z, R¹ and R² are as defined in claim 1,
with a compound of formula (III):

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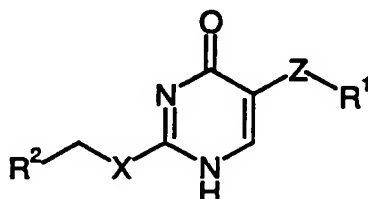


(III)

in which R³, R⁴ and R⁵ are as defined in claim 1; under amide forming conditions;

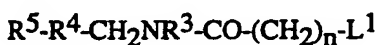
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(b) reacting a compound of formula (IV):



(IV)

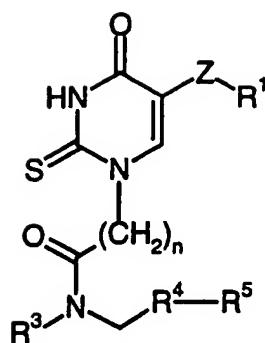
20 in which X, Z, R¹ and R² are as defined in claim 1,
with a compound of formula (V):



(V)

25 in which n, R³, R⁴ and R⁵ are as defined in claim 1, and L¹ is a leaving group such as halogen;
in the presence of a base such as a secondary or tertiary amine, in an inert solvent;

(c) when X is S, reacting a compound of formula (VI):



(VI)

in which n , Z , R^1 , R^3 , R^4 and R^5 are as defined in claim 1,
with a compound of formula (VII):

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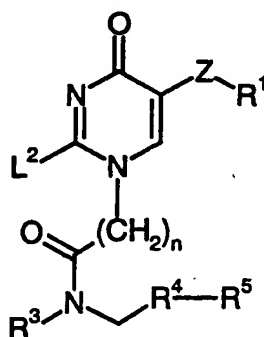


(VII)

in which R^2 and L^1 are as defined in claim 1,
in the presence of a base such as a secondary or tertiary amine, in an inert solvent; or

10

(d) when X is O , reacting a compound of formula (VIII):



(VIII)

15 in which n , Z , R^1 , R^3 , R^4 and R^5 are as defined in claim 1, and L^2 is a leaving group,
with a compound of formula (IX):



(IX)

20 in which R^2 is as defined in claim 1,
in the presence of a base, in an inert solvent.